ORPHAN MEDICINAL PRODUCTS

Legal & Regulatory Framework
Development: Challenges and Pitfalls

Dr Françoise de Crémiers

November 4, 2015

Table of content

General considerations

ORPHAN DISEASES

- Life-threatening or chronically debilitating diseases with a low prevalence and a high level of complexity
- 6000-8000 rare diseases have been identified
- 80% are of genetic origin and 50% affect children
- **These diseases affect ≈250 million people worldwide**
- An orphan drug is one that has been developed to treat one of these rare conditions
- From a regulatory perspective **criteria differ between regions**
  - In the U.S., any disease affecting fewer than 200,000 people is considered orphan
  - In the EU, any disease affecting fewer than five in 10,000 person
  - In Japan, less than 50,000

WHY FOSTERING DRUG DEVELOPMENT IN RARE DISEASES?

- Persons suffering from rare diseases have the **same rights** as their European fellow citizens **to benefit from high quality, safe and effective therapies**

GLOBAL OVERVIEW

- 1983: United States - ‘Orphan Drug Act’
- 1993: Japan - ’Orphan Drug Legislation’
- 1998: Australia - ‘Orphan Legislation’
- 1999: Europe - ‘Orphan Regulation’

Orphan Regulation - overview

WHY AN EU ORPHAN REGULATION ?

- Rare diseases: development and marketing **costs are unlikely to be covered** by the expected sales

- Pharmaceutical industry does not develop medicines for rare diseases under normal market conditions

Objective of the EU Orphan Regulation

- Provide **incentives** that stimulate research and development (PUSH)
- Modify market conditions (PULL)
- Set up a system of recognition for orphan drugs entitled for incentives

EU Orphan Regulation

- **Regulation (EC) N° 141/2000** of the EU Parliament and of the Council on Orphan Medicinal Products of 16 December 1999

- For medicinal products for **human use only** ,which excludes Medical Devices, Food and food supplements, and medicinal products for veterinary use

- **Other important features**
  - Criteria for designation
  - Committee (COMP)
  - Procedure
  - Incentives

EU Orphan Regulation – the legal framework

- Commission Regulation (EC) N° 847/2000 of 27 April 2000
- Commission communication July 2003 (2003/C 178/02)
- Commission communication on Art 8(1) & (3) (2008-4077)
- Point to consider document on calculation and reporting of the prevalence of a condition for OD designation (COMP/436/01)

- Provides **incentives for research, development and placing orphan products on the market**
- Establishes a Committee from Member States (**COMP**), patient association representatives and allows for **expert advice** on specific orphan diseases
- Defines **criteria for orphan designation**

EU Orphan Regulation – the legal framework

- **Guidance** – Recommendation on elements required to support the **medical plausibility** and the assumption of **significant benefit** for an orphan designation EMA/COMP/15893/2009 ➔ currently under review

- **Guidance** – guideline on the **format and content** of applications for designation as orphan medicinal products

- **Guidance** – How to apply for an orphan designation on the **EMA webpage**

EU Orphan Designation

- Procedure free of charge – **90 day procedure**
- Apply **at any stage during** development before the MAA
- Sponsor can be either an **individual or a company** based in the EU Community (EU,Ice,Liech,Nor)

- **Criteria**
  - **RARITY (prevalence) / RETURN OF INVESTMENT**
    - Medical condition affecting not more than 5 in 10,000 persons in the Community (around 250,000)
    - Without incentives it is unlikely that the marketing of the product would generate sufficient return to justify the necessary investment
  - **SERIOUSNESS**: Life –threatening or chronically debilitating
  - **SIGNIFICANT BENEFIT/NON SATISFACTORY**
    - If another product is authorised, justification by the sponsor of the product of patient benefits

OD Designation criteria – some important details

- **Medical Condition : EC Guideline (ENTR/6283/00**)
- Recognised **distinct medical entities** are generally considered valid conditions
- Defined in terms of their **specific characteristics** e.g. pathophysiological,histopathological,clinical characteristics
- Different degrees of severity or stages of a disease are generally not considered as distinct conditions

OD Designation criteria – some important details

- Preliminary preclinical and/or clinical data are generally required to support **the medical plausibility** of the medicinal product.
- Pharmaceutical concept is not considered sufficient by regulators
- **45% were based on nonclinical data and the rest were based on data from ongoing or completed clinical studies** (COMP 2014 – 196 positive opinions)

OD Designation criteria – some important details

Medically plausible subset

- Usually defined by characteristics of the drug that **limit the use** of the investigational medicinal product in only the subset of the patients with the disease: *well-defined and justified subset of a well-defined medical condition*
- Subset is **medically recognisable**
- Drug **will not be effective/safe** for the **rest o**f patient population not included in the subset

OD Designation criteria – some important details

- In many cases the true prevalence is not known and will be based on an **estimated prevalence**

- **Critical aspects** of an Application are:
  - the strategies for identifying prevalence data, evaluating and combining available evidence (methodology and sources for prevalence calculations).
  - the conclusion on the population prevalence made by sponsor

Useful Guidance – Point to consider document on calculation and reporting of the prevalence of a condition for OD designation (COMP/436/01)

Orphan Drug Designation (ODD) : Significant Benefit (SB)

Definition:

- '*A clinically relevant advantage or a major contribution to patient care*'
- Based on assumptions at the time of ODD
- Justification why existing methods are not satisfactory
- **SB to be confirmed prior to MA** to maintain Orphan status
- Recommendation document on data for SB and plausibility
- Guideline currently under revision by the EC

Orphan Drug Designation (ODD) : Significant Benefit (SB) - EXAMPLES

- Drug has a new mechanism of action leading to potentially better efficacy
- More convenient administration route (major contribution to patient care)
- Better safety profile but not theoretical risks
- **Higher level of evidence required at time of MA** compare to time of OD designation (in line with stage of development)

- ➔ to be justified

Orphan drug designation: incentives

- **Main EU incentives**

- **Ten year marketing exclusivity** from the MA date granted in all MS (+**2years** for paediatrics)
- Protocol Assistance from EMA
- *EMA/FDA parallel scientific advice*
- Direct /Mandatory Access to Centralised Procedure (CP)

Orphan drug designation : incentives

- *Eligibility to accelerated assessment/approval procedures (CP)*
- Additional support and financial incentives available to companies qualifying for micro, small and medium-sized entreprises (**SME)status**
- Fees reduction for the CP granted by EMA
- **Priority Access to EU research programs**.

Incentives: US vs. EU

- Incentives of Orphan Designation:
  - Waived PDUFA application fees (FY2014 fee ~ $2.5 Million)
  - Annual federal tax credits of 50% of clinical investigations expenses
  - Grant support for product development
  - Protocol assistance in drug development process
  - Exempt from PREA (Pediatric Research Equity Act) requirements
- Incentive of Orphan Product Approval:
  - Marketing Exclusivity-7 years attached to indication upon approval

- Market Exclusivity
  - Ten years exclusivity from the date of marketing authorization (+ 2 year if pediatric)
  - Unlike the U.S. regulations, marketing exclusivity can be *reduced* to six years if after five years the criteria for designation are no longer met or the profits being made on the product are considered unreasonable
  - Breaking the exclusivity: if the similar product is clinically superior
- Fee reduction / exemption
- Protocol assistance
- EU-funded research

OD Designations and approvals

- **US** (June 2015)
  - 3451 Orphan Designation Request Granted
  - 494 Orphan Drugs approvals in the US
  - 41 orphan drugs indications approved in 2014
  - 12 orphan drug indication already by May 2015

- **EU** (Jan 2015)
  - 1400+ Orphan Designation Request Granted
  - 194 (14%) for pediatric indications
  - 100 orphan MAA granted for 81 conditions (including extension of indications/variations)

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf
and http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm

Orphans and Paediatrics

Pediatric Rare Disease Drug Development

Number of Challenges

- A majority of rare diseases are **genetic in origin**, they significantly affect the pediatric population. Yet, as a group**, children comprise a smaller percentage of the overall population**, making it especially **difficult to recruit adequate numbers of pediatric patients**
- Often, even though there may be evidence of safety and effectiveness in adults, there is a **lack of sufficient information about medical product safety and effectiveness in pediatric populations.**
- Additional considerations include the **ethical concerns** related to clinical testing in children and the **need to test in different pediatric sub-groups** (e.g., age, maturation of organ function).
- Last but not least, **deficiencies in the pediatric clinical research infrastructure** (an issue in the development of medicinal products for rare diseases in general) can be a key challenge to the planning of clinical trials for pediatric patients

NICE unconvinced of Duchenne drug benefit

DAILY NEWS | OCTOBER 16, 2015

T 1 Share 10

SELINA MCKEE

Cost regulators for health technologies funded by the National Health Service in England and Wales have rejected a novel treatment for the genetic condition Duchenne Muscular Dsytrophy, seeking more data from the firm to confirm its benefit and justify its high cost.

Related Links

EMA: 39 human-use drug OKs in first -half 2014

First-ever Duchenne drug heads CHMP opinions

PTC Therapeutics' Translarna (ataluren) is the first licensed treatment for DMD that addresses the loss of dystrophin, the underlying cause of the condition, with current treatment options in England 'merely' focusing on alleviating symptoms and managing complications. But the current standard of care - corticosteroid therapy - can cause side effects such as growth retardation, bone thinning and weight gain, underscoring the need for alternatives.

Translana has been awarded a conditional marketing authorisation in the UK for treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in patients who are able to walk aged five years and older. Around eight to 13 boys are born with this condition in the UK every year.

But, while NICE has recognised that the drug represents "an important development in the treatment of DMD and could potentially prolong the time before children have to use a wheelchair", draft guidelines produced by its Highly Specialised Technologies arm seek further clarification on the magnitude of the benefit, and ask that data from the ongoing confirmatory study (designed to back full approval) are provided as soon as possible.

NICE backs four drugs for rare childhood arthritis

DAILY NEWS | OCTOBER 23, 2015

T 0 Share 7

SELINA MCKEE

The National Institute for Health and Care Excellence has published final draft guidelines recommending four drugs to treata form of arthritis in children and young people.

Related Links

Roche's RoActemra gets EU OK for rare child arthritis

EU regulators expand license of Pfizer's Enbrel

SMC 'yes' for Roche's RoActemra, 'no' for Gilead's Cayston

The Institute has provisionally recommended Bristol-Myers Squibb's Orencia (abatacept), AbbVie's Humira (adalimumab), Pfizer's Enbrel (etanercept) and Roche RoActemtra (tocilizumab), within their marketing authorisations, as options for treating juvenile ideopathic arthritis (JIA).

Around 10,000 children and young people in the UK are affected by JIA, an umbrella term that describes a group of conditions involving joint inflammation lasting longer than six weeks in children aged under 16 years, causing pain, swelling and limitation of movement.

US - Pediatric Rare Disease Priority Review Voucher Program

- **Rare Paediatric Disease**
  - "Primarily affects individuals from birth to 18 years" AND
  - Is a "rare disease or condition" (e.g affect fewer than 200,000 in the US)
- **"Rare Paediatric Disease Product Application" – NME**
  - Regulated under 505(b)(1) or 351(a)
  - Eligible for priority review
  - Relies on clinical data from studies in a paediatric population
  - Does not seek approval for an adult indication
- **Consists of 2 components:**
  - Designation as a "rare paediatric disease"
    - Voluntary
    - Not a pre-requisite to be eligible for a PRV (**P**riority **R**eview **Vo**uchers)
    - Administered by OOPD (**O**ffice of **O**rphan **P**roducts **D**evelopment)
  - Determination of voucher
    - eligibility Whether NDA or BLA satisfies criteria for a "rare pediatric disease application"
    - Administered by individual review divisions in CDER & CBER
    - If designation not sought, OOPD consulted as to whether disease is a "rare paediatric disease"
- **Sunset provision – approval before March 17, 2016 ➔ will this be reconducted under the 21st Cures Bill?**

Applying for an orphan drug designation

The ODD Application

- Consult the relevant **guidances**
- Submitted **references** should be current and relevant
- **Prevalence** should be justified (supportive analysis)
- Comprehensive abbreviation list
- To be engaged with the pre-submission process & taking on board the scientific advice.

Orphan drug designation: **procedure**

- Letter of Intent to file (according to EMA predefined timelines) at least 2 months prior the planned submission
- Pre-submission meeting at EMA
- Application submission
- Validation of the contents of the application
- **DAY 1**: Evaluation
- **DAY 60**: COMP meeting providing an opinion and a list of questions/oral explanation
- **DAY 90**: COMP meeting granting an opinion leading to a decision

The ODD Application : key components

- Details of the **condition**
- Proposed orphan **indication**
- **Medical plausibility**
- Justification of **severity**
- **Prevalence** of the condition
- **Return on investment**
- **Existing methods** of treatment
- Justification why methods not satisfactory
- Justification of **significant benefit**
- Summary of development
- Current regulatory status
- Bibliography

Committee for **O**rphan **M**edicinal **P**roducts (COMP)

- **EMA Committee**
- 1 elected chair (Prof. Bruno Sepodes, PT)
- 1 elected vice-chair (Ms Lesley Green, Eurordis patient representative) – for 3 years
- 1 Representative per Member State
- 3 Patients' Representatives appointed by the EU Commission
- 3 Members appointed by the EU Commission
- 1 Member for Norway, 1 Member for Iceland
- 1 EU Commission representative
- General observers
- +/-experts & patients for specific products

Committee for **O**rphan **M**edicinal **P**roducts (COMP)

COMP is responsible for

- Opinions on orphan designation
- Advising on general EU policies
- International cooperation
- Monthly meetings (except August)

Orphan Drugs - development challenges

Orphan Product Development Challenges (1/2)

Scientific challenges

- Limited natural history and science knowledge
- Challenge of **designing appropriate clinical development program**
- Difficulty identifying experts and sufficient number of patients for clinical studies
- Silo approach in scientific efforts, divided by disease

Rare Diseases in Children Pose Unique Challenges

- Paediatric drug dosing challenges
  - Often involve adjusting adult doses **based on a child's decreased weight**, without considering potential age-based differences in drug metabolism and toxicities
- Recruitment for the conduct of successful clinical trials
- Ethical consideration

Orphan Product Development Challenges (2/2)

Regulatory challenges

- Applying the **similar regulatory standards** for an indication with small # of patients as for an indication with large # of patients. **Statistical power** of the study a problem
- Sometimes **not possible to do double-blind studies**
- Often **lack of hard clinical endpoint**
- Expertise limitations impacting regulators' review of rare diseases applications

Commercial

- Unique business models
- Reimbursement and pricing - challenge of striking the balance

Orphan Medicinal Products

- **Development challenges** :

- In terms of **quality**
- In terms of **non clinical**
- In terms of **clinical efficacy**
- In terms of **clinical safety**

Orphan Medicinal Products : **quality** development challenges

- In order to perform a valuable clinical trial to be included into the MA submission package,a **proper formulation is needed**
- **Quality** testings identified and reproducible
- **Stability** testings being considered

- The CMC/ Quality document should be included into the Clinical Trial Application (CTA).

Orphan Medicinal Products : **non clinical** development challenges

- Non clinical development should be considered as needed and be presented to EMA during the Protocol technical assistance (Briefing Document).

Questions and proposed answers can be raised in this area.

Orphan Medicinal Products : **clinical efficacy** development challenges

- **Scientific limitations** due to:
- The **rarity** of the disease : low patient enrollment
- The **targeted** patient definition criteria
- The **subset** of patients should be medically recognizable
- The **primary end-point** selection: pronostic factors or disease course indicators might not be known
- The difficulty to design a statistically powerful study : **sample size**

Orphan Medicinal Products : **clinical efficacy** development challenges

- Two studies not feasible (small number of existing patients)
- **Use of placebo**

- justification of not giving the existing treatment if any

- When the disease creates dommages, how can we justify withdrawing concurrent treatment ?

Orphan Medicinal Products:clinical **safety** development challenges.

- **Safety assessment** difficult due to the rarity of the disease, the limited patient population exposure at the time of MAA (post-MA committments)- low number of patients.
- Risk Management Plan to be included into the MAA

Assisting the Orphan Drug Development

Assisting the OD development - EMA

- **Protocol Assistance :** Art. 6 of Regulation (EC) N° 141/2000
- Protocol Assistance: Scientific Advice for Companies developing Orphan Medicinal Products
  - CHMP/SAWP & COMP representatives with experts and patients' representatives
  - F2F meeting
- Sponsors asks questions on Quality aspects, Preclinical development, clinical development, clinical safety (RMP) and other regulatory aspects
- Draft clinical study synopsis can be discussed

FDA/EMA parallel Scientific Advice

- A useful opportunity to streamline product development and facilitate access to orphan drugs, paediatrics and products eligible for accelerated review (breakthrough products)
- Increase inter agency dialogue
- Allow identification of critical regional issues/needs as a joint advice cannot be achieved
- At the request of the sponsor

FDA/EMA Parallel Scientific Advice

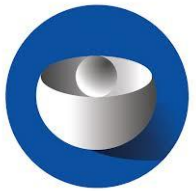
- Clear Eligibility criteria regarding the procedure - transparency
- Justification in case of non-acceptance with rationale.
- List of issues/topics for discussion rather than detailed questions
- Identification of specific regional needs or commonalities early in the development
- Organizational arrangements

FDA/EMA Parallel Scientific Advice

- A global Industry conclusion : Information sharing and perspectives.
- The procedure is a very positive step forward and should be used more often – limited uptake by companies
- Involvement of both Agencies at the same time
- Visibility of each other's concerns and regional requirements
- Time and resource savings over separate possibly sequential meetings
- Allow to progress very quickly with the development program based on advices received from both Agencies, likely at the same time

FDA/EMA Parallel Scientific Advice

- FDA&EMA will discuss on issues raised : pre and post-meetings.
- The Company will be part of the discussion in a second step via a TC, videoconference, or at the Agency site (EMA or FDA)
- Meeting minutes will be issued separately by FDA and EMA: **individual regulatory decision-making**.
- Clarifications and follow-up scientific advice will be possible
- More information: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf



Orphan Drugs and MAA registration Procedure

Orphan Medicinal Products: MAA

- The MAA is based on same standards as for non orphan products (quality, safety, efficacy)
- Submission via the **Centralised Procedure only**
- **CHMP** is responsible for assessment and **final opinion**
- Authorisation within designated OD condition
- More than OD designation possible per product (independent incentives)
- Designation shall be removed if it is established PRIOR to granting the MA that designation criteria are no longer met (Art.5.12 Reg. 141/2000)
- COMP will review 'significant benefit' criterion prior to CHMP opinion

Orphan Medicinal Products: MAA Specific requirements (1/2)

Assessment of similarity (WHEN ORPHAN IS ON MARKET)

- Applies if other orphan medicines authorised for the same designated condition
- Need to submit report in Module 1.7: molecular structure, mechanism of action, similarity of indication (overlap of populations ?)
- CHMP assessment by competent WP
- CHMP final opinion
- Similarity can be triggered at any time before EC Decision
- Proactive publication during ongoing procedures

Orphan Medicinal Products: MAA Specific requirements (2/2)

Maintenance designation criteria

- Report to be submitted to Orphan medicines section: at time of MAA possibility to OD report update
- Need to address ALL designation criteria
- Standard set at time of Authorisation
- Assessment of OD updated Report by COMP
- COMP opinion **after** the CHMP opinion

Orphan Medicinal Products : MAA Procedure

- Sponsor submits the OD updated Report at the same time than the MAA
- Procedure allows TWO discussions at COMP
- COMP adopts opinion only after the CHMP has adopted the opinion for MA
- Possibility to invite sponsor for oral explanation
- COMP opinion can be subject to appeal
- Final COMP opinion sent to the EU Commission

Transparency

OD – Public information

Information available on EMA website

- COMP agenda and monthly report
- Public summary of positive/negative opinion for OD after decision
- EU Commission Register of Orphan designated products after decision
- Position on the removal of a designated orphan medicinal product from the Community Register
- Link to EPAR once product is approved

EMA confidentiality agreements

- **With the US FDA** - Common procedures for applying OD and submitting ANNUAL REPORTS on the status of development of designated orphan medicines

- **With the Ministry for Health, Labour and Welfare (MHLW) in Japan**

- With **Patient organisations** e.g. through the European Organisation for Rare Diseases (EURORDIS)

Pricing and Reimbursement

Pricing and reimbursement of Orphan Medicinal Products

- Follow the same pathway as any other Medicinal Product in **each** of EU Member Sates (HAS for France, NICE for UK…)
  ➔ Price and access vary between countries

- The monopolistic power of OD results in high prices

- Small number of patients: OD are unlikely to provide value for money

- Reimbursement decisions based in some countries on additional criteria (seriousness, alternative therapies, cost to patient..)

Pricing and reimbursement of Orphan Medicinal Products

- **A low prevalence** of a certain orphan indication does not equal a low return on investment for the drug ACROSS its indications

- **High quality evidence** about clinical added value of OD is rarely available at the time of MA due to the low number of patients

- **Post commitment** required to continue research (patient registries to evaluate the longer-term effectiveness and cost-effectiveness - limitations)

Point to consider when developing an Orphan Some recommendations

Orphan Drug Development: Points to Consider (1/2)

Plan to address orphan drug development challenges

- Limited natural history and scientific knowledge
- Challenge of designing appropriate clinical development program: i.e., small populations, diverse collection of disorders, endpoints not validated, etc..
- Expertise limitations: experts and FDA reviewers

Orphan drugs are held to the same statutory requirements for demonstrating effectiveness and safety

- Still need to demonstrate "substantial evidence of effectiveness", with flexibility in how that is achieved, as many of orphan clinical development program are unique (ex. 1 pivotal study)

Consider collaboration and partnership

- Partnering with the FDA and EMA
  - Early and frequent dialogue on development plan
  - Utilizing FDA / EMA CHMP meetings/ interactions
- Collaborating with academia, KOLs and patient advocacy groups

Consider global spectrum of orphan drug development, i.e., Japan and Australia

Orphan Drug Development: Points to Consider (2/2)

- Obtain Orphan **Designation early** in drug development
- Most important is **partnering with the Health Authorities**
  - Early and frequent dialogue on your drug development plan
  - Taking full advantage of interactions available and optimize these opportunities
- **Collaborating with academia, KOLs and patient groups**
  - To better understand the disease
  - Help design appropriate clinical studies
  - Identify patient population
- Utilizing available regulatory frameworks

Abbreviations

CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
EC	European Commission
EMA	European Medicines Agency (www.ema.europa.eu)
EURORDIS	European Organisation for rare diseases (www.eurordis.org)
FDA	Food and Drug Administration (www.fda.org) - US
HAS	Haute Autorité de Santé
KOL	Key Opinion Leader
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MHLW	Ministry for Health, Labour and Welfare - Japan
NICE	National Institute for Health and Care Excellence
OD	Orphan Drug/Designation
SAWP	Scientific Advice Working Party